

### REMARKS

In response to the office action dated June 9, 2009, Applicants have corrected a typographical error in the specification and added new claims 27-29. Support for new claim 27 can be found *at, e.g.*, page 18, lines 16-22 of the specification. Support for new claim 28 can be found *in, e.g.*, Table 1 of the specification. Support for new claim 29 can be found *at, e.g.*, page 10, lines 26-28 of the specification. Claims 1-4, 8, 9, 12-15, 20, and 25-29 are presented for examination.

#### Rejections under 35 U.S.C. §103(a)

The office action rejects claims 1-4, 8, 9, 12-15, 20, 25, and 26 as unpatentable on three grounds, each of which is traversed below.

#### I

Claims 1-3, 8, 9, 13, 14, and 20 are rejected under 35 U.S.C. §103(a) as obvious from Nishiguchi et al., U.S. Patent No 6,046,040 ("Nishiguchi I") in view of Huang et al., *Adv. Synth. Catal.* 343 (6-7), 2001, 675-681 ("Huang") with evidentiary support from Ni et al., *Chinese Chemical Letters*, 18 (2007), 79-80.

Independent claim 1 is discussed first. Claim 1 recites a polymer containing (i) 20 to 80 mol% of (meth)acrylic acid residue; (ii) 0.1 to 50 mol% of a first vinyl monomer residue containing a sugar chain and a linker, in which the sugar chain contains a monosacharride or an oligosaccharide residue and the linker contains a selectively cleavable bond; and (iii) at least a second vinyl monomer residue different from the (meth)acrylic acid residue and the first vinyl monomer residue. Applicants found that by adjusting the percentage of the (meth)acrylic acid residue to 20 to 80 mol% and adjusting the percentage of the first vinyl monomer residue to 0.1 to 50 mol%, the density of sugar chains in the polymer can be controlled so that the polymer thus obtained exhibited a high sugar transfer efficiency when used as a primer during a glycosylation reaction. *See, e.g.*, Table 1 on page 44 of the specification.

Nishiguchi I describes a method for producing a glycoconjugate that includes binding a sugar residue to the side chain of a water-soluble polymer via a linker having a selectively cleavable linkage to give a primer, and bringing the primer into contact with an immobilized

glycosyltransferase in the presence of a sugar nucleotide to transfer a sugar residue of the sugar nucleotide to the sugar residue of the primer. *See, e.g.*, the abstract. However, as correctly pointed out by the Examiner, Nishiguchi I does not disclose or render obvious a polymer containing 20 to 80 mol% of (meth)acrylic acid residue, as recited by claim 1. In addition, Nishiguchi I does not disclose or render obvious a polymer containing three different monomer residues (*i.e.*, the (meth)acrylic acid residue, the first vinyl monomer residue, and the second vinyl monomer residue) and 0.1 to 50 mol% of the first vinyl monomer residue, as recited by claim 1.

The office action asserts that it would have been obvious to combine Huang with Nishiguchi I to provide the polymer recited in claim 1 allegedly because Huang suggests that increasing the amount of acrylic acid in a thermo-responsive polymer would increase the lower critical solution temperature (LCST) of the polymer, which would facilitate a glycosylation reaction using this polymer as a primer. However, as discussed in Applicants' reply filed on April 29, 2009, Huang describes in Figure 1 the LCSTs of support polymers that are used to immobilize an enzyme (not a sugar residue as recited in claim 1) and do not contain acrylic acid as recited in claim 1. Although Huang describes in Scheme 1 polymers (*e.g.*, polymer 7) that contain a sugar chain and acrylic acid, it does not discuss the effect of the amount of acrylic acid on the LCSTs of these polymers.

The office action states (at page 9, last paragraph) that

Huang does teach a polymer containing acrylic acid (see structure 7 on page 677) and it does teach the effect of LCST on the activity of a primer (pages 677-678). The NASI units in the polymers in Figure 1 (p. 676) are converted to acrylic acid units as shown in the steps of making the structure 7 on page 677.

However, although Huang discloses (on page 677) polymer 7 that includes acrylic acid and a sugar chain, nowhere does Huang discuss the relationship between the amount of acrylic acid and the LCST of polymer 7. Indeed, Figure 1 is the only place in Huang that describes the relationship between the LCSTs of polymers and the compositions of the polymers. However, the polymers described in Figure 1 on page 676 contain N-isopropylacrylamide (NIPAM), N-t-butylacrylamide (NTBAM), and N-acrylylsuccinamide (NASI), not acrylic acid. Further,

although NASI can be converted to acrylic acid, it is well known that acrylic acid is much more hydrophilic than, and therefore significantly different from, NASI. Thus, it would have been apparent to one skilled in the art that the relationship between the LCST of a polymer containing NASI and the amount of NASI in such a polymer is significantly different from the relationship between the LCST of a polymer containing acrylic acid and the amount of the acrylic acid in such a polymer.

The office action alleges that

The effects of the LCST of the polymer which is part of a primer construction are also disclosed. Thus, 'we present our studies of enzymes attached to such polymers as recyclable biocatalysts and enzymatic carbohydrates synthesis with **glycosyl acceptors immobilized on the polymer through a cleavable linker**. Due to the high solubility of oligosaccharides in water and the high cost of enzymes, it is desirable to carry out enzymatic synthesis in such systems, which would **allow the recovery of enzymes and products by gentle heating after the reaction.**' (p. 675). An example of subjecting the primer 7 to a galactosylation reaction followed by precipitating the polymer by heating to 55°C is also given (p. 678, left column).

See the paragraph bridging pages 9 and 10; emphases in original. However, the passage on page 675 in Huang quoted by the office action merely describes a potential advantage of using the system studied by Huang. It clearly does not mention any relationship between the amount of acrylic acid in the a polymer and the LCST of the same polymer, let alone the effect of an increase in the amount of acrylic acid in a polymer on the LCST of the polymer. Further, the passage in left column, page 678 in Huang quoted by the Examiner at most suggests that the polymer 8 (which is a product of a galactosylation reaction of polymer 7) has a LCST lower than 55°C<sup>1</sup>, but does not discuss whether increasing the amount of acrylic acid in polymer 8 would increase the LCST of this polymer, as asserted by the office action.

In sum, Huang does not teach any relationship between the LCST of a polymer and the amount of acrylic acid in the polymer. Thus, it would not have been obvious to combine Huang with Nishiguchi I to provide the polymer recited in claim 1.

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<sup>1</sup> Huang describes that a thermo-responsive water-soluble polymer would be soluble in water when the water temperature is lower than the LCST of the polymer. See the introduction.

Even if Huang and Nishiguchi I somehow were combined, the result would still not have been the polymer recited in claim 1. Indeed, Nishiguchi I is entirely silent on a polymer containing a (meth)acrylic acid residue, let alone a polymer containing 20-80 mol% of a (meth)acrylic acid residue as recited in claim 1. Huang describes a polymer 7 having 0.6 parts of a residue containing a sugar residue, 0.4 parts of an acrylic acid residue, 10 parts of isopropyl acrylamide residue. However, the acrylic acid residue in polymer 7 is only about 3.6 mol% ( $0.4 / (0.6 + 0.4 + 10) \approx 3.6 \text{ mol\%}$ ), much less than 20-80 mol% of a (meth)acrylic acid residue as recited in claim 1. Thus, even if Huang and Nishiguchi I somehow were combined, the result at most would have been a polymer containing about 3.6 mol% of acrylic acid, which is not the polymer recited in claim 1.

In addition, nothing in Huang would have prompted one skilled in the art to raise the amount of acrylic acid in polymer 7 described in Huang from about 3.6 mol% to 20 mol%, the lower limit of the amount of a (meth)acrylic acid residue recited in claim 1. Indeed, when discussing the LCST of a polymer containing a sugar residue, Huang teaches that “[t]he LacNAc bearing polymer 8 was also sialylated using  $\alpha$ -2,3-sialyltransferase (Scheme 2). Due to the highly hydrophilic nature of the sialyl-LacNAc, the LCST of the polymer becomes higher than 90°C so that the polymer cannot be recovered by raising the temperature of the solution.” See the paragraph bridging page 678-679; emphasis added. Thus, Huang teaches that it is not desirable to raise the LCST of a polymer containing a sugar residue at least because it would be difficult to isolate such a polymer from a reaction solution. Further, a polymer with a high LCST requires a high precipitation temperature for isolation, which would deactivate the enzyme used in the glycosylation reaction, thereby defeating one of the objects that Huang intends to achieve (*i.e.*, recovering the enzyme used in the glycosylation reaction). Thus, one skilled in the art, in view of the teachings in Huang, would not have wanted to raise the amount of acrylic acid in a polymer containing sugar residues from about 3.6 mol% to 20 mol% as recited in claim 1 to increase its LCST.

Ni does not cure the deficiencies in Nishiguchi I and Huang. Ni was published in 2007, at least 3.5 years after the earliest priority date of the present application, *i.e.*, May 8, 2003. Thus, Ni does not qualify as prior art or evidentiary support. Indeed, at the time the present

application was filed, one skilled in the art would not have had access to the information described in Ni.

Even if Ni somehow qualifies as prior art or evidentiary support (which Applicants do not concede), it still does not cure the deficiencies in Nishiguchi I and Huang. Specifically, the office action asserts (page 4, 2<sup>nd</sup> last paragraph) that

It is well known in the art that in a thermo-responsive copolymer such as random copolymer of N-isopropylacrylamide (NIPAM) and acrylic acid (AA), increasing the content of the acrylic acid will increase the LCST of the copolymer. (See Ni, Figure 1). Thus, if an intended enzymatic reaction is done at, say 35°C, a copolymer of NIPAM and AA having about 10 mol% of AA would have LCST lower than 35°C (i.e., it is insoluble at that temperature) and it is therefore not beneficial to the reaction.

However, it is well known that an enzymatic reaction should be carried out at a low temperature due to the lack of stability of an enzyme under heat. Indeed, Huang discloses that its galactosylation reaction of polymer 7 is carried out at room temperature, not at 35°C as asserted by the office action. *See* Scheme 1, condition (g) and page 679, right column, last paragraph. Further, Ni describes an NIPA-AA polymer containing about 5.7 mol% AA (i.e.,  $0.06 / (1 + 0.06) \approx 0.57$  mol%) and an NIPA-AA polymer containing about 8.3 mol% AA (i.e.,  $0.09 / (1 + 0.09) \approx 0.83$  mol%). *See* Fig. 1. The LCSTs of these two polymers are respectively about 33°C and about 35°C, both of which are higher than room temperature. Thus, contrary to the office action's assertion, the polymers described in Ni would be soluble in water (i.e., the solvent for the galactosylation reaction described in Huang) at room temperature (i.e., the temperature for the galactosylation reaction described in Huang). It follows that it would not have been necessary for one skilled in the art to raise the amount of AA in the polymers described in Ni from about 5.7 mol% or 8.3 mol% to 20 mol% as recited in claim 1. Indeed, doing so would not likely improve the solubility of the polymer described in Ni in water at room temperature, but would only make the product of the galactosylation reaction (which would have a high LCST) more difficult to isolate. Further, a product having a higher LCST requires a higher precipitation temperature for isolation, which would deactivate the enzyme used in the galactosylation

reaction, thereby defeating one of the objects that Huang intends to achieve (*i.e.*, recovering the enzyme used in the glycosylation reaction).

For at least the reasons set forth above, claim 1 would not have been obvious from Nishiguchi II in view of Huang and Ni. As claims 2, 3, 8, 9, 13, 14, and 20 depend from claim 1, they also would not have been obvious from Nishiguchi I in view of Huang and Ni.

To complete the record, Applicants add the following comments to certain statements made in the office action.

The office action asserts that “[f]irst, the optimum temperature for certain enzyme-catalyzed reactions is higher than ambient temperature.” *See* the office action, page 10, last paragraph. As discussed above, Huang describes an enzyme-catalyzed galactosylation reaction at room temperature. Further, neither Nishiguchi I nor Ni describes an enzyme-catalyzed reaction. In other words, none of the three references cited in this rejection describes an enzyme-catalyzed reaction that is carried out at a temperature higher than ambient temperature, as asserted by the office action.

The office action also asserts that “[t]hird, in such polymer, increasing the content of acrylic acid will increase the LCST. Such effect of acrylic acid on the LCST of a thermo-responsive copolymer is well known in the art, such as in Huang (Table in Figure 1, Polymers A and B), and in Ni (above).” *Id.* However, as discussed above, Polymers A and B described in the table in Figure 1 in Huang include N-acrylylsuccinamide (NASI), but do not include acrylic acid. Acrylic acid is much more hydrophilic than and significantly different from NASI. Thus, the effect of NASI on the LCST of a polymer containing NASI is significantly different from the effect of acrylic acid on the LCST of a polymer containing acrylic acid. Further, although Huang describes polymer 7 containing acrylic acid, it simply does not disclose the effect of acrylic acid on the LCST of this polymer. In addition, Ni does not qualify as prior art or evidentiary support. Even if Ni somehow qualifies as prior art or evidentiary support (which Applicants do not concede), it still does not provide any motivation to one skilled in the art to raise the amount of acrylic acid in polymer 7 described in Huang to 20 mol% as recited in claim 1.

Finally, the office action asserts that

[fourth], it would have been obvious to a person of ordinary skill in the art to employ the acrylic acid-containing copolymers taught by Huang, with

higher content of acrylic acid, in the process taught by [Nishiguchi I, Nishiguchi II, and Yamada] as a primer carrier for a glycosylation reaction at elevated temperature so that the polymer is soluble in the reaction temperature (which results in increased product yield) and is insoluble when the temperature is increased (which facilitates product isolation).

*Id.* However, the acrylic acid-containing polymer described in Huang (*e.g.*, polymer 7) is soluble in water at the temperature (*i.e.*, room temperature) used to carry out its glycosylation reaction. *See, e.g.*, page 679, right column, last paragraph. It follows that it would not have been necessary for one skilled in the art to raise the amount of acrylic acid in the polymers described in Huang to increase its LCST, let alone raising the amount of acrylic acid to 20 mol% as recited in claim 1. Indeed, doing so would not likely improve the solubility of Huang's polymer in water at room temperature, but would only make Huang's glycosylation product (which would have a high LCST) more difficult to isolate. Further, a glycosylation product having a high LCST requires a high precipitation temperature for isolation, which would deactivate the enzyme used in the glycosylation reaction, thereby defeating one of the objects that Huang intends to achieve (*i.e.*, recovering the enzyme used in the glycosylation reaction).

## II

Claims 1-3, 12-15, and 20 are rejected under 35 U.S.C. §103(a) as obvious from Nishiguchi et al., JP 2001-220399 ("Nishiguchi II") in view of Huang with evidentiary support from Ni.

Independent claim 1 is discussed first. As discussed above, claim 1 recites a polymer containing (i) 20 to 80 mol% of (meth)acrylic acid residue; (ii) 0.1 to 50 mol% of a first vinyl monomer residue containing a sugar chain and a linker, in which the sugar chain contains a monosaccharide or an oligosaccharide residue and the linker contains a selectively cleavable bond; and (iii) at least a second vinyl monomer residue different from the (meth)acrylic acid residue and the first vinyl monomer residue.

Nishiguchi II describes glycopeptides that can include monosaccharide residues. *See, e.g.*, claim 1. Like Nishiguchi I, Nishiguchi II does not disclose or render obvious a polymer containing three different monomer residues (*i.e.*, the (meth)acrylic acid residue, the first vinyl monomer residue, and the second monomer residue), which include 20 to 80 mol% of the

(meth)acrylic acid residue and 0.1 to 50 mol% of the first vinyl monomer residue, as recited by claim 1.

As discussed above, neither Huang nor Ni cures the deficiencies in Nishiguchi II. It would not have been obvious to combine Nishiguchi II with Huang and Ni to provide the polymer recited in claim 1. Even if the cited references were somehow combined, the result would still not have been the polymer recited in claim 1.

Thus, claim 1 would not have been obvious from Nishiguchi II in view of Huang and Ni. As claims 2, 3, 12-15, and 20 depend from claim 1, they also would not have been obvious from Nishiguchi II in view of Huang and Ni.

### III

Claims 1-4, 8, 9, 13, 14, 20, 25, and 26 are rejected under 35 U.S.C. §103(a) as obvious from Yamada et al., Carbohydrate Research 305 (1998), 443-461 ("Yamada") in view of Huang with evidentiary support from Dalkas et al., *Polymer* 47 (2006) 243-248.

Independent claim 1 is discussed first. As discussed above, claim 1 recites a polymer containing (i) 20 to 80 mol% of (meth)acrylic acid residue; (ii) 0.1 to 50 mol% of a first vinyl monomer residue containing a sugar chain and a linker, in which the sugar chain contains a monosacharride or an oligosaccharide residue and the linker contains a selectively cleavable bond; and (iii) at least a second vinyl monomer residue different from the (meth)acrylic acid residue and the first vinyl monomer residue.

Yamada describes copolymerizing glycomonomers (which includes sugar residues) with acrylamide to give glycopolymers, which can be used in sugar elongation reaction in the presence of a glycosyl transferase. *See, e.g.*, the abstract. Like Nishiguchi I and II, Yamada does not disclose or render obvious a polymer containing three different monomer residues (*i.e.*, the (meth)acrylic acid residue, the first vinyl monomer residue, and the second monomer residue), which include 20 to 80 mol% of the (meth)acrylic acid residue and 0.1 to 50 mol% of the first vinyl monomer residue, as recited in amended claim 1.

As discussed above, Huang does not teach any relationship between the LCST of a polymer and the amount of acrylic acid in the polymer. Thus, there would not have been any reason to combine Yamada with Huang to provide the polymer recited in amended claim 1.



The office action relies on Dalkas to show that homopolymer of acrylamide (a comonomer used in Yamada) is highly soluble in water and is therefore not thermo-responsive. The office action then proceeds to conclude that use of only acrylamide in Yamada's glycopolymers does not work toward facilitating efficient separation of the products from the reactants because the separation cannot be achieved simply by changing the temperature to precipitate either the products or the reactants. *See* the office action, page 8, 2<sup>nd</sup> paragraph.

First, Dalkas was published in November, 2005, more than two years after the earliest priority date of the present application, *i.e.*, May 8, 2003. Thus, Dalkas does not qualify as prior art or evidentiary support. Indeed, at the time the present application was filed, one skilled in the art would not have had access to the information described in Dalkas.

In addition, Yamada discloses that its products (*i.e.*, glycoconjugates) can be obtained in high yield by cleaving the linker between the support polymer and the sugar residues. *See, e.g.*, the abstract. It would have been apparent to one skilled in the art that it is unnecessary for Yamada's glycopolymers to be thermo-responsive to facilitate separation of Yamada's products. Thus, it would not have been obvious to insert acrylic acid residues mentioned in Huang into the glycopolymers described in Yamada to adjust the solubility of Yamada's glycopolymers.

Finally, even if Huang and Yamada somehow were combined, the result at most would have been a polymer containing only about 3.6 mol% of acrylic acid, which would still not have been the polymer recited in claim 1.

Thus, claim 1 would not have been obvious from Yamada in view of Huang and Dalkas. As claims 2-4, 8, 9, 13, 14, 25, and 26 depend from claim 1, they also would not have been obvious from Yamada in view of Huang and Dalkas.

### New Claims

Applicants submit that new claims 27-29 are patentable over the cited references.

Specifically, claims 27-29 depend from claim 1 and, therefore, are patentable over the cited references for at least the reasons set forth above.

Claim 28 is patentable over the cited references on an additional, independent ground. In particular, claim 28 recites a polymer containing 10 to 70 mol% of the second vinyl monomer

residue. None of the cited references discloses or renders obvious such a polymer. Thus, claim 28 is patentable over the cited references on this additional, independent ground.

### CONCLUSION

Applicants submit that this application is now in condition for allowance, which action is requested.

Any circumstance in which Applicants have: (a) addressed certain comments of the Examiner does not mean that Applicants concede other comments of the Examiner; or (b) made arguments for the patentability of some claims does not mean that there are not other good reasons for the patentability of those claims and other claims.

According to the communication issued on June 22, 2009, the USPTO has restarted the time period for replying to the present office action due to its delay in loading the office action in the Image File Wrapper system. Specifically, the time period for replying to the present office action now commences on the notification date of the communication, *i.e.*, June 22, 2009. Thus, the new due date for filing a reply without an extension is September 22, 2009. Accordingly, Applicants have submitted herewith a Petition for One-Month Extension. The extension fee in the amount of \$130.00 is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization.

Please apply any other charges to deposit account 06-1050, referencing Attorney's Docket No. 18900-0003US1.

Respectfully submitted,

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